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The purpose of these studies is to determine factors affecting blood pressure (BP) maintenance during hemorrhage and the consequences on O_2 delivery (O_2del). The scope covers the cardiovascular, oxygen delivery, and hormonal responses to hemorrhage while breathing hyperoxic, normoxic and hypoxic air mixtures, in conscious goats. Additionally, the role of the hormonal responses, particularly vasopressin (AVP) and angiotensin II, on the cardiovascular and O_2del responses is being investigated. We have shown that a controlled hemorrhage at 0.5 ml/kg/min for 30 min conducted in the same goats while exposed to either 11, 21, and 100% FIO_2, reduced mean arterial BP by approximately 25, 15, and 5 mmHg respectively. Improved maintenance of BP during hyperoxia was achieved, in part, by an earlier rise in systemic vascular resistance, and O_2 consumption was similar in all experiments following hemorrhage. Presence of the spleen did not affect the magnitude of drop in BP, O_2del, nor hormonal responses to the hemorrhage during normoxic conditions. Other experiments involved responses to i.v. infusions of AVP during 11 or 21% FIO_2. AVP increased the arterial O_2 concentration during hypoxia as expected, but the AVP-induced decrease in cardiac output prevented an improvement in O_2del. Neither hypoxia nor the rate of AVP infusion affected whole body AVP clearance.

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J. R. [illegible] 15 Aug 1997

PI - Signature Date

TABLE OF CONTENTS

INTRODUCTION

When the tissues of the body receive too little O_2 to maintain adequate function, various reflexes respond causing increased respiration and cardiac output. Depending on the cause of the reduced O_2 the systemic vasculature can constrict or dilate. In response to hypoxia, for instance, cardiac output is increased and systemic vascular resistance is reduced (1). This allows for increased flow of blood to the tissues, improved O_2 delivery, and maintenance of normal blood pressure. In the case of hemorrhage, however, the body is also faced with reduced O_2 at the tissues, but by reflexes mediated primarily via low pressure system baroreceptors, an increased sympathetic tone results leading to vascular constriction and increased heart rate (2). This allows the system to maintain blood pressure with hemorrhages up to about 15% of total blood volume, thereby maintaining perfusion pressure and circulation to select areas of the body. Near this volume of hemorrhage, however, there is a sympathetic inhibition. This appears to initiate the life threatening conditions of decreasing mean arterial blood pressure and heart rate with any further loss of blood.

It can be hypothesized from this background, that if hemorrhage were to occur during hypoxia that there would be a conflict of reflexes, hypoxia causing a vasodilatation and hemorrhage causing a vasoconstriction. In fact, this has been recently shown. Eichinger and Claybaugh (3) reported an earlier reduction in blood pressure during a controlled hemorrhage in goats during exposure to hypoxia, 10 % inspired O_2, than when breathing a normoxic gas mixture. This has subsequently been confirmed in experiments using rats that were hemorrhaged either during acute exposures to hypoxia (12% O_2) or after a chronic, 3-week exposures to hypoxia (4). Only the acute exposure to hypoxia was associated with the decreased ability to maintain blood pressure during hemorrhage. Moreover, the chronic exposures increased threshold of volume of blood loss required to elicit a fall in blood pressure in both the normoxic and hypoxic states (4,5). The mechanism of the latter is unknown.

It could also be hypothesized that if hypoxia causes a decreased ability to maintain blood pressure, that hyperoxia may reduce or eliminate the reduction in mean arterial blood pressure in response to a modest hemorrhage. However, the vasoconstrictor effects of hyperoxia may adversely affect oxygen delivery to certain areas of the body. Therefore, as one objective of these studies, we investigated and compared the ability to maintenance arterial blood pressure during hemorrhage under conditions of normoxia, hyperoxia and hypoxia. In addition, measurements of systemic vascular resistance, O_2 delivery and O_2 consumption were determined.

A second objective of this proposal was to further investigate the effects of vasopressin on O_2 delivery and O_2 consumption. It has been known for many years that vasopressin can be released by stimulation of chemoreceptors (6). Furthermore, hypoxic stimulation of vasopressin appears very early in development, and has been reported in fetal sheep during the third trimester (7). While there exists strong evidence for a role of vasopressin as causal in the often fatal condition of high altitude cerebral edema, and possibly high altitude pulmonary edema (8), there has been a paucity of information concerning the possible beneficial role of vasopressin in the response to hypoxia. Intuitively, it would seem that such an early, ontogentically, developed response, that is present in many if not all mammals, would have some survival value. In previous studies in our laboratory (9,10) we have shown that exogenous, intravenously administered, vasopressin greatly improves PaO_2, SaO_2, and shunt fraction in the anesthetized, artificially ventilated, new born piglet, especially during hypoxic conditions. This response has

not been confirmed in a conscious, spontaneously breathing animal. The adult goat model presently being used in our laboratory was very suitable for these experiments, because, in conjunction with local anesthesia, the jugular vein is readily accessible introduction of a Swan-Ganz catheter for the necessary measurements. In addition, the multiple infusion rates of vasopressin and subsequent plasma levels of vasopressin achieved allowed an opportunity to further study the whole body clearance of vasopressin. It has been previously shown to be positively correlated with plasma levels of vasopressin in dogs and humans (11). This is the first study to determine the effects of hypoxia on the whole body clearance of vasopressin.

Lastly , the role of the spleen in animals with contractile spleens, has been thought to be that of a reservoir of blood. Therefore, in studies involving hemorrhage in animals with contractile spleens, the spleen is often removed, presumably so the animal will respond more like a human, because humans do not have contractile spleens (12). The spleen, however, may have other effects. For instance, Horton et al. (13) have reported evidence that dogs with their spleens intact, respond to hemorrhage with greater myocardial contractility than splenectomized dogs with or without augmented infusion of blood to mimic the effects of the spleen. Similar studies have not been done in the goat, nor on the modest rate and magnitude of hemorrhage that we have employed in this conscious standing animal. Therefore, in order to better understand the role of the spleen in our animal model we investigated the cardiovascular responses and the O_2 delivery and consumption and hormonal responses in the intact and splenectomized goat.

The third major objective of the proposal will focus on central control mechanisms that affect the maintenance of blood pressure and cardiac output during hemorrhage. Specifically we will be testing the hypothesis that central mechanisms that are responsible for the sympathetic withdrawal are mediated either directly or influenced by vasopressin. These experiments are in progress and no preliminary findings are available. Since the writing of this proposal, Budzikowski et al. (14) have reported that blockade of central V1 receptors for vasopressin abolished the hemorrhage-induced bradycardia and hypotension in WKY (Wistar Kyoto) rats, but not in SHR (Spontaneously Hypertensive Rats). Our studies, currently underway, are therefore very important in establishing whether this response is more generalized to the mammalian population, and if so, we will be able to assess the mechanism of the maintained blood pressure, i.e. cardiac output or systemic vascular resistance or both.

BODY:

The remainder of this report will deal with studies already completed. The remaining studies are in the initial stages and are being conducted as originally described in the proposal.

Experimental Methods:

Young adult female goats, weighing about 30-45 kg, have been used. We have recently acquired some neutered male goats, which will be used in the experiments in the second half of the project. This protocol was approved by the Tripler Army Medical Center Institutional Animal Care and Use and Committee, and the facility and program are AAALAC approved.

All goats have been prepared with an exteriorized carotid arterial loop, as described earlier (3), at least 3 weeks before any experiments. This allows repeated access to the artery for

purposes of arterial pressure recordings, heart rate, arterial blood gas and cooximetery measurements, hormone samples, and blood removal for hemorrhage.

On the experiment day, the goats were placed in a stanchion and the areas of the carotid loop and the contralateral jugular vein were shaved and swabbed with antiseptic. The carotid artery was cannulated and the line connected to a pressure transducer and recorder. After local anesthesia, a small skin incision was made over the jugular vein, and an introducer was inserted into the jugular vein, and a Swan-Ganz catheter was inserted through the introducer into the jugular vein and advanced to the pulmonary artery. Location was determined by monitoring the pressures at the tip and at the point used to measure central venous pressure (CVP), while advancing the catheter. With these catheters in place, we measured mean arterial pressure (MABP), and the systolic and diastolic pressures, heart rate, CVP, pulmonary arterial pressure (PAP), pulmonary arterial wedge pressure (PAWP), and cardiac output (CO) was determined by thermodilution.

Infusions were made via the port to the area of the right atrium in the Swan-Ganz catheter, and blood removal was from the arterial or from the Swan-Ganz catheter depending upon whether arterial or venous blood was needed. With assessments of O_2 content by cooximetery and blood gas analysis on the arterial venous sides, and having measured cardiac out put, calculated values of O_2 delivery and O_2 consumption and of systemic vascular resistance and pulmonary arterial resistance were obtained.

In experiments where hypoxic or hyperoxic gas mixtures were administered, either air, air diluted with nitrogen (hypoxia), or 100% O_2 was delivered through a face mask through a one-way valve, from compressed gas cylinders. The fractional inspired O_2 (FIO_2) was constantly monitored and flow meters were adjusted to deliver either 11%, 21%, or 100% O_2 .

Hemorrhage was performed by removal of blood with a peristaltic pump calibrated to remove 0.5 ml/kg/min. The blood was collected in sterile blood donor bags containing citrate. At the conclusion of the experiment the blood was returned to the animals.

Splenectomy was performed via a left paracostal approach originally described for splenectomy in sheep (15).

Experimental designs:

Hyperoxia series: Six goats were hemorrhaged 0.5 ml/kg/min while exposed to normal air, 11% O_2 or, 100% O_2. Control measurements were obtained 60 minutes after cannulation, and then the inspired gas mixture was begun. After 30 min of breathing the prescribed gas mixture, the pre-hemorrhage measurements were obtained. Hemorrhage was then begun, with measurements obtained at 10 min intervals up to 30 min. At this time the experiment was concluded and the hemorrhaged blood was returned.

Arginine vasopressin (AVP) infusion series: Six goats were infused with AVP at various doses while breathing either 11% or 21% O_2. A set of measurements was obtained 60 minutes after cannulation. The breathing gas was then initiated, and normal saline (vehicle) was infused for 20 min and the second set of measurements was obtained. The third through the seventh measurements were obtained following 20 min periods of AVP infusion at 30, 100, 300, 1000, 3000 pg/kg/min in that order.

Splenectomy series: Six goats had blood volumes assessed by the Evan's Blue dye dilution technique before and after splenectomy. They also were hemorrhaged before and after splenectomy similar to the protocol described above in the "Hyperoxia series". Following the hemorrhage experiments in the spleen-intact condition, the surgery was performed and the second hemorrhage was conducted a minimum of 3 weeks later, and within 2 months of the first experiment.

Statistics: There were six goats in each series. The same goats were in each exposure, and sampled over several periods. Therefore, the Analysis of Variance (ANOVA) design used was a one-way with repeated measures where each goat would have 3 times the measures as was used in one exposure. For instance, in the data of figure 1, the data were analyzed as a 6 (goat) by 15 (treatments) table. When the F value for the ANOVA was significant, the means of interest were compared by post hoc analysis with a Fisher's LSD Multiple-Comparison test. The statistical software used was NCSS version 6.0.21 (Copyright 1996, Dr. Jerry L. Hintze, Kaysville, Utah).

Results and Discussion:

Hyperoxia series:

As hypothesized, the fall in mean arterial pressure in response to 30 min of hemorrhage at 0.5 ml/kg/min was dependent upon the concentration of O_2 in the inspired air (Figure 1).

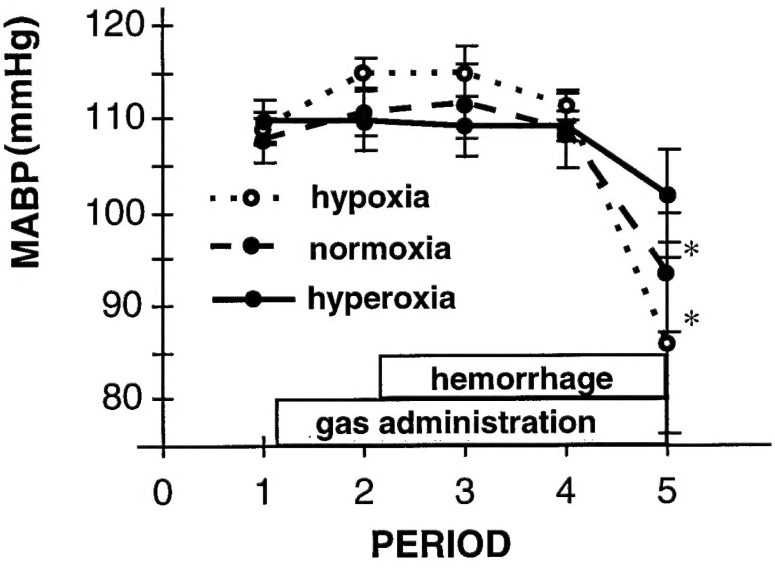

Figure 1. Response of mean arterial blood pressure to hemorrhage of 0.5 ml/kg/min. Period 1 = 60 min post cannulation, 2 = 30 min following initiation of either 11 %, 21% or 100% FIO_2, 3 = 10 min of hemorrhage, 4 = 20 min hemorrhage, 5 = 30 min hemorrhage. * = $P < 0.05$ compared to period 1.

It is noteworthy that with this magnitude of hemorrhage, 15/ml kg, inspiration of 100% O_2 prevented the fall in MABP, where both normoxic and hypoxic conditions were accompanied by

significant decreases. Very recent work by others appearing in an abstract has described a similar response in rats while breathing 100% O_2 following hemorrhage (16). Our work focused further on O_2 delivery and consumption. It was anticipated that 100% O_2 might improve the maintenance of arterial blood pressure, but at what consequence to O_2 distribution to the tissues? Decreased O_2 consumption (VO_2) may be an index of poor perfusion of tissues or perhaps the reduced work involved in breathing. Regardless, VO_2 did decrease with the initiation of 100% O_2 breathing (Figure 2). However, during hemorrhage the VO_2 returned

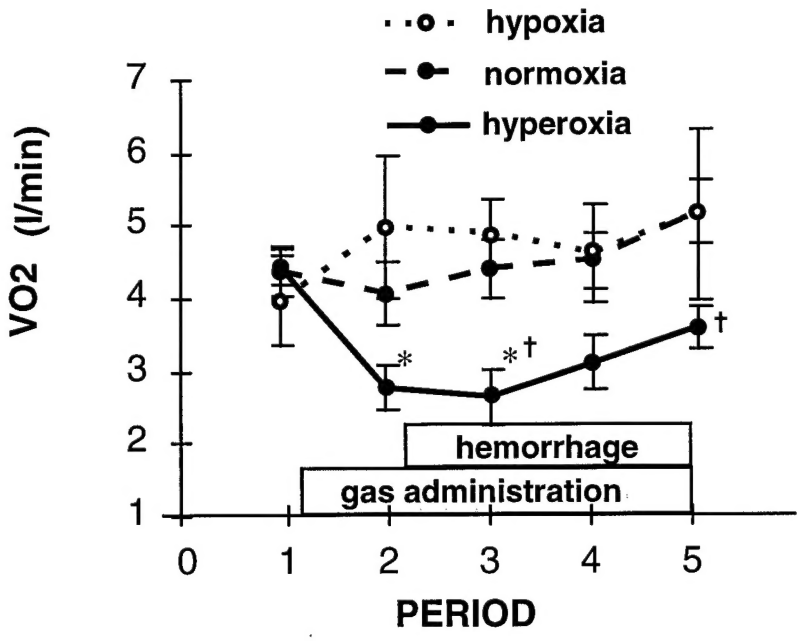

Figure 2. O_2 consumption (VO_2) during hemorrhage in conscious goat while breathing 11%, 21% or 100% O_2. The periods are the same as described for Fig.1., * = $P<0.05$ compared to period 1, † = $P < 0.05$ compared to normoxic conditions.

toward baseline, but VO_2 was still significantly below the values observed while breathing hypoxic or normoxic gases. Since the gap in VO_2 between hyperoxic and normoxic gas breathing appears to remain constant as VO_2 increases during hemorrhage, it is tempting to speculate that the cause for the reduction does not change. If this is the case, then hyperoxia does not compromise the necessary circulation to provide O_2 to those areas of demand during hemorrhage. Therefore, administration of 100% O_2 may be a safe and physiologically useful adjunct to emergency first aide to patients during hemorrhage, because of its ability to maintain perfusion pressure. Regional blood flow distribution studies will be necessary to assess the validity of this speculation.

We also hypothesized that, due to stimulation of chemoreceptors by hypoxia, that the vasopressin response to hemorrhage might be altered. Vasopressin was increased during the last period in all situations, but was significantly blunted during hyperoxia. This is expected because of the differences in MABP (Fig 1). However, subsequent regression analysis between MABP and plasma AVP indicated similar slopes with all breathing gas mixtures. In contrast, the low pressure system, as measured by right atrial pressure, was also correlated with plasma AVP

levels, and hyperoxia was shown to significantly reduce the plasma AVP response to reduced stretch of the low pressure system baroreceptors. Vasopressin alters the regional distribution of blood flow, greatly favoring blood flow to the brain and heart, while shunting it away from the kidney, spleen, muscle, and skin (17). Thus, the reduced vasopressin response during hemorrhage during hyperoxia may work against its beneficial effects.

Clearly more work is needed to sort out the beneficial from potentially harmful effects of 100% O_2 administration during hemorrhage, but our results favor a beneficial effect.

Arginine vasopressin (AVP) infusion series:

The infusion of AVP into goats either while breathing hypoxic or normoxic gas mixtures resulted in nearly identical plasma levels of the hormone at all doses. Therefore, hypoxia resulted in no difference in AVP clearance as we had hypothesized based on earlier experiments in the neonatal piglet. However, exogenous administration of AVP did result in an increased PaO_2 (Figure 3). Note the significant improvement of PaO_2 at the highest infusion rate of AVP.

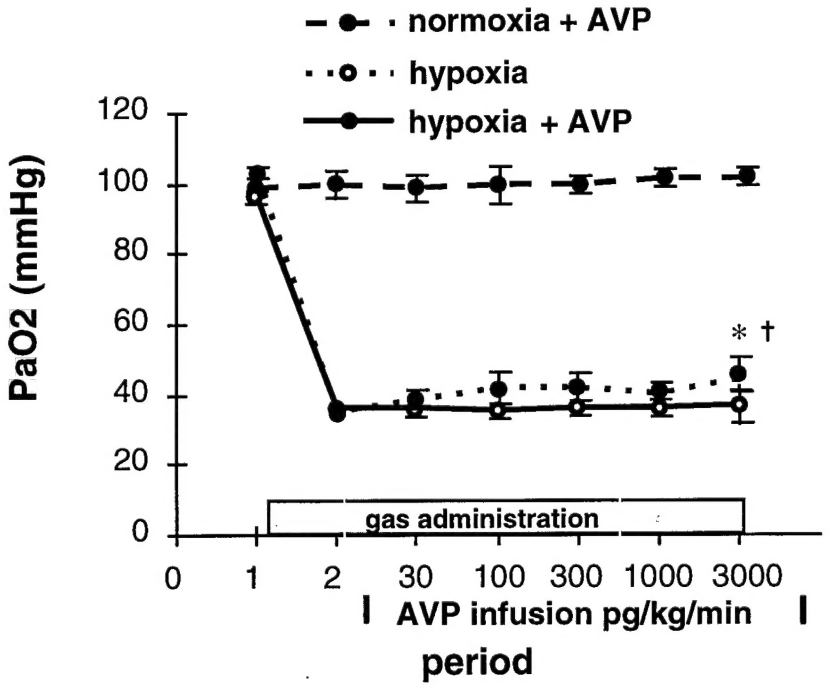

Figure 3. Effect of AVP infusion on PaO_2 during hypoxia and normoxia. Periods 1 and 2 are control periods 60 after catheterizations, and 30 min after initiation of 11% or 21% FIO_2 . AVP infusion rates are shown on the x axis, each infusion period was 20 min. * = $P<0.05$ compared to period 2. † = $P < 0.05$ compared to hypoxia without AVP infusion.

This improved PaO_2 was in association with a 10% improvement in arterial hemoglobin saturation ($P<0.05$), but because of the well documented effects of AVP in decreasing cardiac output, O_2 delivery was not significantly improved. Never-the-less the effects of AVP on PaO_2 were confirmed in this model, albeit a modest response. In previous work in the anesthetized

piglet model, we were able to infuse LVP (lysine vasopressin) at much higher doses (100 ng/kg/min), but these doses would not be tolerated in the conscious goat. Thus, the dose may have contributed to more obvious response we observed in the piglet. The present experiments, however, demonstrate that this response can be achieved by physiological levels of plasma AVP. In these experiments the plasma AVP levels were approximately 135 uU/ml in both infusion experiments which is frequently observed during hypotensive hemorrhage.

Splenectomy experiments:

Changes in MABP, cardiac output, and systemic vascular resistance were essentially identical when hemorrhage was performed before and after splenectomy. In addition, the hormone responses of vasopressin and renin were very similar. The most outstanding difference in the cardiovascular responses was the heart rate response shown below (Figure 4).

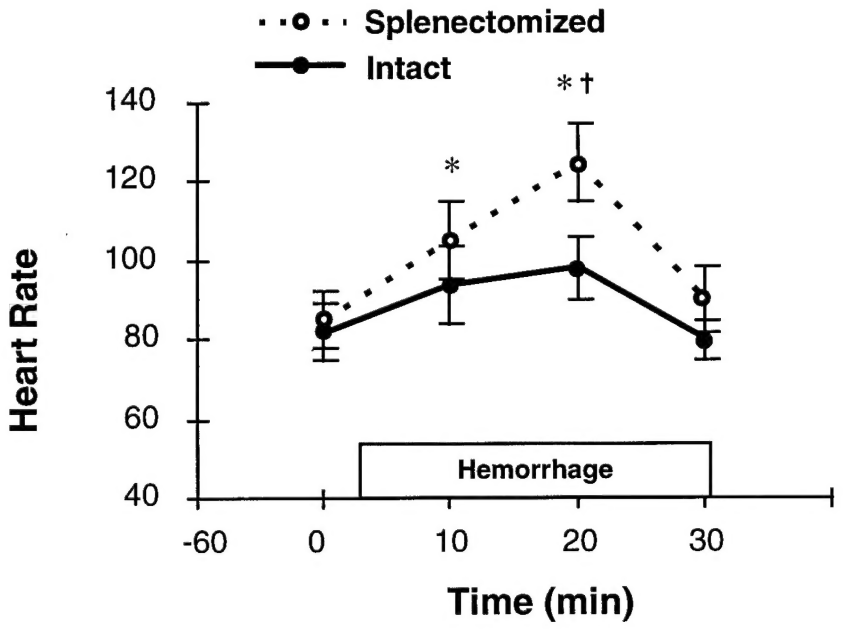

Figure 4. Effect of splenectomy on the heart rate response to hemorrhage (0.5 ml/kg/min). * = P<0.05 compared to pre-hemorrhage value. † = P < 0.05 compared intact condition.

Since the cardiac output was unchanged as a consequence of splenectomy, it would seem that stroke volume (SV) would have to be reduced in the splenectomized condition. In fact, mean values were lower, albiet not statistically significant, and this was due to a slightly reduced central venous pressure (CVP), also not significantly lower than in the intact state. Since hematocrit was significantly increased during the 20 and 30 minutes of hemorrhage, it would appear that the spleen was ejecting some volume of red blood cells into the circulation. This

added volume may have contributed to the slightly improved CVP and SV during hemorrhage in the intact goat. Furthermore, it is likely that the inability to maintain SV in the splenectomized goat, reflexly resulted in increased sympathetic drive to maintain CO and adequate O_2 delivery. At this level of hemorrhage, in this model, the consequences of splenectomy on CO, O_2 delivery and consumption, and on hormonal responses to volume of hemorrhage was indiscernible.

CONCLUSIONS:

The work in this project has produced the following findings: 1) Administration of 100 % O_2 during hemorrhage will help to maintain mean arterial blood pressure without compromising O_2 consumption. 2) Vasopressin improves PaO_2 during hypoxia, albiet very slightly, at physiological levels of plasma AVP. Also, hypoxia does not seem to alter the whole body clearance of AVP compared to the normoxic condition. 3) Splenectomy altered the responses to a slightly hypotensive hemorrhage in ways that lead to a clear difference in heart rate. Apparently owing to a reduced filling pressure, SV was not as well maintained as in the intact condition; however, CO was maintained by the increased heart rate. The mechanisms for this adjustment can not be determined from our data. These studies have been presented in the following abstracts:

Claybaugh, J.R., A.K. Sato, and C.F.T. Uyehara. Effects of vasopressin (VP) on the cardiopulmonary responses to hypoxia in the conscious, spontaneously breathing, goat. Experimental Biology 94. Abstract #4778, FASEB J. 8:A824, 1994.

Claybaugh, JR, Sato, AK, Van Scoy, SC. Effects of Hyperoxia and hypoxia on cardiopulmonary and hormonal responses to hemorrhage. Experimental Biology '95, (Abstract # 1535), FASEB J. 9: A265,1995.

Urada. K.K., Claybaugh, J.R., and Sato A.K., Splenectomy alters the normal response to a hemorrhage in the goat. Experimental Biology '97. New Orleans, LA. April 6-10, 1997. FASEB J.11:A462, 1997 (Abstract #2675).

Lastly, this grant has provided stipend support for K.K. Urada for his predoctoral research, it provided considerable training experience for Dr. S.C. VanScoy, a neonatal fellow in our laboratory for 3 years. Mr Urada is progressing well in his thesis research, and Dr Van Scoy sucessfully completed his fellowship and passed his boards. Manuscripts for the three completed studies are in various stages of preparation. The work developed in reference citation (3), and in the first abstract above, have resulted in an invition for a Symposium on Sports Science at the '97 Winter Olympics in Nagano Japan this October.

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